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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 659 174 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
10.02.1999 Bulletin 1999/06

(21) Application number: **94923915.6**

(22) Date of filing: **06.07.1994**

(51) Int Cl.[6]: **C07C 237/12**, C07C 237/22, C07C 233/01, A61K 31/16, A61K 31/275, C07C 255/25

(86) International application number:
PCT/US94/07498

(87) International publication number:
WO 95/01956 (19.01.1995 Gazette 1995/04)

(54) DERIVATIVES OF VALPROIC AND 2-VALPROENOIC ACID AMIDES AND USE AS ANTICONVULSANTS

2-PROPYLVALERIANSÄURE UND 2-PROPYLVALERIAN-SÄUREAMID-DERIVATE UND DEREN VERWENDUNG ALS ANTIKONVULSIVE MITTEL

DERIVES D'AMIDES D'ACIDE VALPROIQUE ET D'ACIDE 2-VALPROENOIQUE ET LEUR UTILISATION COMME ANTICONVULSIVANTS

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **06.07.1993 US 88074**

(43) Date of publication of application:
28.06.1995 Bulletin 1995/26

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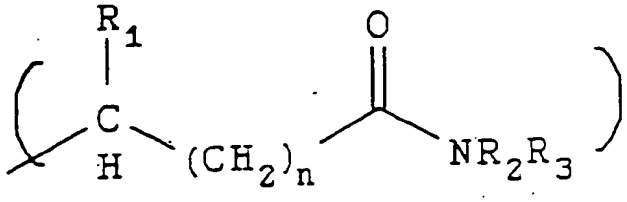
(56) References cited:
EP-A- 0 046 707
BE-A- 885 303
FR-A- 2 531 950

- **CHEMICAL ABSTRACTS, Vol. 101, No. 17, issued 22 October 1984, GRANNEMAN, G.R., "Aspects of the Metabolism of Valproic Acid", see Abstract No. 143458y, Xenobiotica 14, (s) pp. 375-87, 194.**
- **XENOBIOTICA, vol.14, no.5, 1984, page 357 - 387, GRANNEMAN ET AL. 'ASPECTS OF THE METHABOLISM OF VALPROIC ACID'**
- **ADVANCED ORGANIC CHEMISTRY, 3rd ed., John Wiley & Sons, 1985, "Reactions, Mechanisms, and Structure", J. March, pp. 354-355, 368, 377-379**

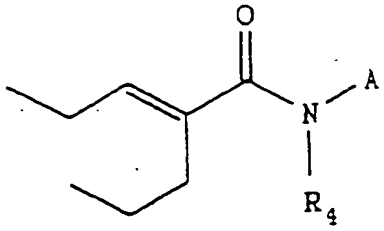
Applicants: Mitchell Shirvan et al.
Serial No.: 09/932,370
Filed: August 17, 2001
Exhibit 12

EP 0 659 174 B1

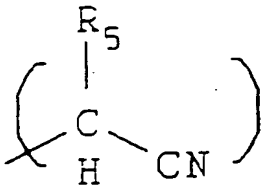


R_1, R_2, R_3, R_4 and R_5 are each independently hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group; and n is 0.

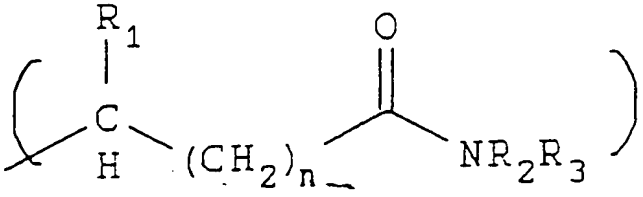
[0007] This invention provides a compound of general formula II as follows:



wherein A is X or Y,
X comprises



Y comprises



R_1, R_2, R_3, R_4 and R_5 are each independently hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group; and n is 0, 1, 2, or 3.

[0008] This invention provides pharmaceutical compositions which comprise a compound of general formula I or II or a pharmaceutically acceptable salt thereof in a therapeutically effective amount and a pharmaceutically acceptable carrier.

Brief Description of the Drawings:

[0009] A more complete understanding of the invention and many of its advantages will become apparent by refer-

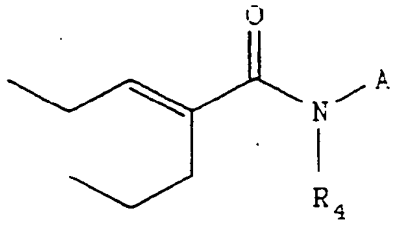
hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group. In still another embodiment, the invention provides the compound of formula I wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

[0015] In preferred embodiments, examples of the compound according to the invention include:

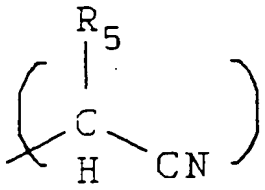
N-(2-n-propylpentanoyl)glycinamide;
N-(2-n-propylpentanoyl)-N-methyl-glycinamide;
N-(2-n-propylpentanoyl)glycine-N'-methylamide;
N-(2-n-propylpentanoyl)glycine-N'-butylamide;
N-(2-n-propylpentanoyl)leucinamide;
N-(2-n-propylpentanoyl)alanine-N'-benzylamide;
N-(2-n-propylpentanoyl)alaninamide;
N-(2-n-propylpentanoyl)-2-phenylglycinamide;
N-(2-n-propylpentanoyl)threoninamide;
N-(2-n-propylpentanoyl)glycine-N',N'-dimethylamide;
and N-(2-n-propylpentanoyl)aminoacetonitrile.

[0016] In addition, novel compounds of general formula II exhibiting high activity and low toxicity are related to those of general formula I, except for having a double bond in the 2-position.

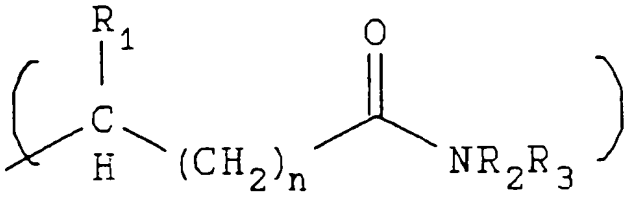
[0017] This invention therefore provides a compound of general formula II as follows:

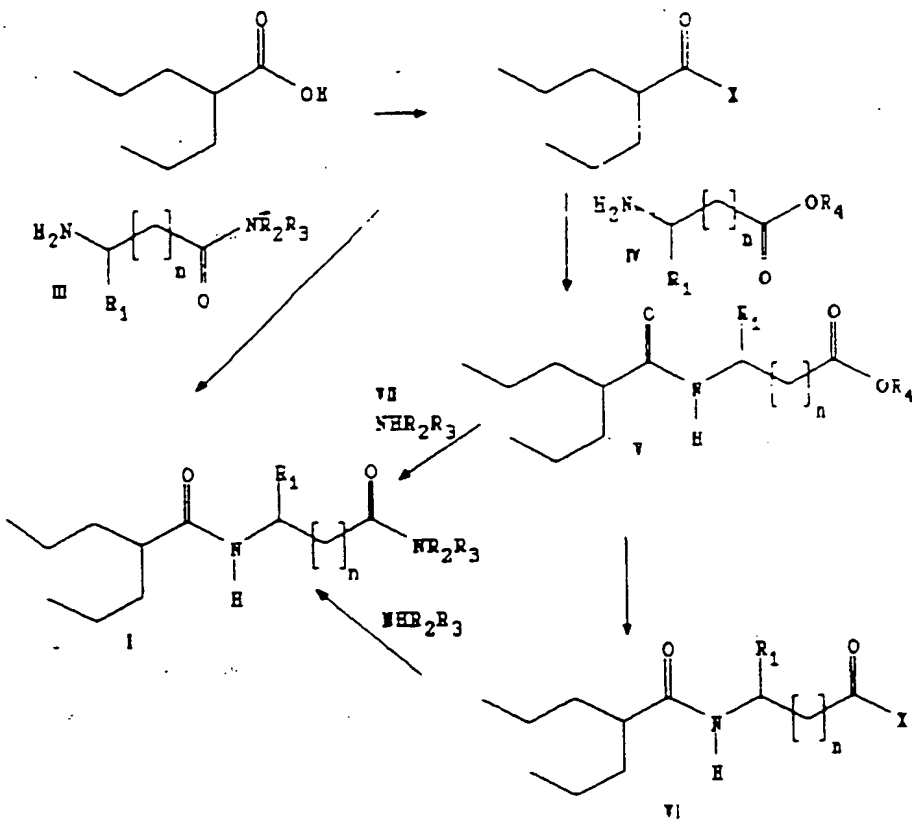


wherein A is X or Y,
X comprises



Y comprises





R_4=H or C_1-C_3 alkyl

X= halide or activated ester, e.g., N-oxysuccinimide

[0027] Thus, compounds I and V may be prepared in a biphasic system consisting of a basic aqueous solution of amino acid amides III or amino acid esters IV and a solution of valproyl chloride in an inert water-immiscible organic solvent, e.g. dichloromethane or toluene, at a temperature ranging between 0 and 50°C, preferably at 0-10°C, for a period of 1 to 24 hrs, preferably 1 to 5 hrs.

[0028] The basic substance employed for the purpose may be either alkali, such as sodium hydroxide, potassium hydroxide, or potassium carbonate, or an aliphatic or aromatic tertiary amine, preferably triethylamine, and must be present in a quantity sufficient to neutralize the hydrohalic acid formed during the reaction.

[0029] Compounds I and V may also be prepared by reacting an activated ester of VPA with amino acid amides III or amino acid ester IV. Thus, VPA is reacted with an activating agent, e.g., N-hydroxysuccinimide, pentafluorophenol, pentachlorophenol, or 1-hydroxybenzotriazole, in the presence of a dehydrating reagent such as a dialkylcarbodiimide, e.g., dicyclohexylcarbodiimide, diisopropylcarbodiimide, or N-(dimethylaminopropyl)-N'-ethyl carbodiimide, at a temperature ranging from 0-50°C, preferably at 0-25°C, in an inert solvent, such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, dichloromethane, or N,N-dimethylformamide. The resulting activated ester may be isolated and purified, or used directly in situ. The activated ester, whether purified or used directly, is reacted with III or IV, under the same conditions leading to condensation as detailed hereinabove.

[0030] The reaction of compounds V with amines R_2R_3NH may be carried out in a wide variety of organic solvents, including in an aprotic solvent which is a saturated or aromatic hydrocarbon, such as hexane, benzene, or petroleum ether, or a halogenated solvent, such as chloroform or dichloromethane, in a protic or alcoholic solvent, such as methanol or ethanol, or water. Preferably, the solvent is methanol. The reaction proceeds effectively at a temperature ranging from ambient to reflux, but preferably at 50-70°C.

[0031] Compounds III may be used either as free bases or as their addition salts, formed by treatment of the free bases with an inorganic acid, such as tetrafluoroboric acid, hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid, such p-toluenesulfonic acid, acetic acid, or benzoic acid. Compounds III may be either a pure enantiomeric form, whether of D or L configuration, or a racemic mixture.

[0032] The amino acid amides and esters of general formulas III and IV are either commercially available or, alter-

[0048] IR: 3410, 3300, 2955, 2925, 1720, 1655, 1645, 1540, 1260 cm^{-1}.

EXAMPLE 3

N-(2-n-Propylpentanoyl)-2-phenylglycinamide.

[0049] A solution of valproyl chloride (1.95g, 12mmole) in 1,2-dimethoxyethane (DME, 30ml) was added to an ice-cooled suspension of phenylglycinamide (1.80g, 12mmole, prepared fromDL-phenylglycinonitrile, Ger. off. 2637204) and Et3N (2.4 g, 24 mmole) in DME (35 ml). The reaction mixture was stirred under a nitrogen atmosphere for 24 hrs at RT, and the resultant product was collected by filtration, washed with cold hexane (50ml) and taken into EtOAc/H20 (200 ml:175 ml). The organic layer was separated, washed successively with satd. NaHCO3, 0.1N HCl and satd. NaCl, dried and evaporated to dryness. The crude product was crystallized from EtOAc, affording 2.50 g (9.06 mmole, 75%) of the title compound as a white crystalline solid, mp 190-1°C.

[0050] Anal. calc. for $C16H24N_2O_2$: C, 69.53; H, 8.75; N, 10.14; Found: C, 68.26; H, 8.57; N, 9.96.

[0051] ^1H NMR δ (DMSO): 8.36 (br d, 1H, CONH), 7.65 (br s, 1H, CONH), 7.46-7.22 (m, 5H, Ph), 7.10 (br s, 1H, $CONH_2$), 5.46 (d, 1H, Ph-CH), 2.44 (m, 1H, Pr_2CH), 1.40, 1.22, 1.10 (m, 8H, $CH_3CH_2CH_2$), 0.85 (t, 3H, Me), 0.78 (t, 3H, Me) ppm.

[0052] MS: 277 (MH^+, 56), 201 (100).

[0053] IR: 3400, 3300, 2950, 2910, 1735, 1685, 1560, 1400 cm^{-1}.

EXAMPLE 4

N-(2-n-Propylpentanoyl)alanine methyl ester.

[0054] A solution of DL-alanine methyl ester hydrochloride (13.7 g, 98 mmole) and Et_3N (20.2 g, 200 mmole) in water (50 ml) was added dropwise to an ice-cooled solution of valproyl chloride (15.0 g, 92 mmole) in CH_2Cl_2 (150 ml). After completion of addition the reaction mixture was stirred for 4 hrs. at RT. The layers were then separated and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were washed successively with water, satd. $NaHCO_3$, 0.1N HCl and satd. NaCl, dried and evaporated to dryness. The residue was treated with hexane (60ml), and the resultant solid was collected by filtration, washed with hexane and dried to give 14.2g (62mmole, 63%) of the title compound as a white solid, mp 72-3°C.

[0055] ^1H NMR δ ($CDCl_3$): 6.02 (br d, 1H, NH), 4.63 (quintet, 1H, ala CαH), 3.75 (s, 3H, OMe), 2.08 (m, 1H, Pr_2CH), 1.6, 1.4, 1.32 (m, 8H, $CH_3CH_2CH_2$), 1.40 (d, 3H, ala Me), 0.89 (t, 6H, Me) ppm.

[0056] MS: 230 (MH^+, 100), 127 (7), 104 (16).

[0057] IR: 3300, 2925, 1740, 1630, 1540 cm^{-1}.

EXAMPLE 5

N-(2-n-Propylpentanoyl)glycine methyl ester.

[0058] The title compound was prepared from valproyl chloride (19.34g, 119mmole) and glycine methyl ester hydrochloride (15.0g, 119mmole), according to the procedure described in Ex. 4. 22g (102 mmole, 86%) of an off-white solid, mp 68°C, was thus obtained.

[0059] ^1H NMR δ ($CDCl_3$): 5.97 (br t, 1H, NH), 4.06 (d, 2H, gly CH_2), 3.76 (s, 3H, OMe), 2.14 (m, 1H, Pr_2CH), 1.60, 1.45-1.25 (m, 8H, $CH_3CH_2CH_2$), 0.90 (t, 6H, Me) ppm.

[0060] MS: 216 (MH^+, 100), 127 (13).

[0061] IR: 3300, 2945, 2920, 1765, 1650, 1550, 1220 cm^{-1}.

EXAMPLE 6

N-(2-n-Propylpentanoyl)alaninamide.

[0062] Aqueous ammonia (25%, 50ml) was added dropwise to a solution of N-(2-propylpentanoyl)alanine methyl ester (6.87g, 30mmole) in methanol (20ml), and the reaction mixture was stirred under reflux for 4 hrs. The solid which precipitated upon cooling was filtered, washed with cold hexane, dried and crystallized from EtOAc to give 1.90g (8.92mmole, 30%) of the title compound as a white crystalline solid, mp 165-166°C.

[0063] Anal calc. for $C_{11}H_{22}N_2O_2$: C, 61.64; H, 10.35; N, 13.08; Found: C, 61.35; H, 10.26; N, 13.32.

[0064] ^1H NMR δ (DMSO): 7.84 (br d, 1H, CONH), 7.21 (br s, 1H, $CONH_2$), 6.92 (br s, 1H, $CONH_2$), 4.25 (quintet,

EXAMPLE 11

N-(2-n-Propylpentanoyl)-4-aminobutyramide.

[0083] To an ice-cooled solution of N-(2-propylpentanoyl)--4-aminobutyroyl chloride (prepared from N- (2-propylpentanoyl)-4-aminobutyric acid and $SOCl_2$, 5.9 g, 24.0 mmole) in dioxane (25ml), was added dropwise conc. NH_4OH (34 ml) over 1 hr. The reaction mixture was then stirred at RT for 20 hrs and evaporated to dryness under reduced pressure. The residue was taken up in an H_2O (20 ml) and EtOAc (30ml) mixture, the mixture stirred vigorously for 5 min. The organic phase was separated, evaporated to dryness under reduced pressure, and the residue crystallized from EtOAc to give 1.4 g (6.1 mmole, 26%) of a crystalline solid, mp 138°C.

[0084] Anal calc for $C_{12}H_{24}N_2O_2$: C, 63.13; H, 10.60; N, 12.27; Found: C, 63.12; H, 10.69; N, 12.54.

[0085] ^{1}H NMR δ (DMSO): 7.81 (br t, 1H, NH), 7.26 (br s, 1H, $(CH_2)_3CO\underline{NH_2}$), 6.73 (br s, 1H, $(CH_2)_3CO\underline{NH_2}$), 3.02 (m, 2H, $\underline{CH_2}CH_2CH_2CONH_2$), 2.11 (m, 1H, $Pr_2\underline{CH}$), 2.03 (t, 2H, $\underline{CH_2}CONH_2$), 1.58 (m, 2H, $\underline{CH_2}CH_2CONH_2$), 1.42 (m, 2H, $\underline{CH_2}CHCO$), 1.19 (m, 6H, $\underline{CH_2CH_2}CHCO$), 0.84 (t, 6H, Me) ppm.

[0086] MS: 229 (MH_+, 100), 127 (17).

[0087] IR: 3405, 3300, 3190, 2960, 2935, 2880, 1660, 1655, 1635, 1550, 1445 cm^{-1}.

EXAMPLE 12

N-[2-n-Propylpent-(E)-2-enoyl]glycinamide.

[0088] A cold solution of glycinamide hydrochloride (6.63g, 60 mmole) in water (18ml) and Et_3N (12.79, 126 mmole) were added slowly to a stirred and ice-cooled solution of (E)-2-ene-valproyl chloride in toluene (40 ml). After completion of addition, the biphasic reaction mixture was stirred at ambient temperature for 3 hrs. Work-up and crystallization according to the procedure in Ex. 1 afforded 6.92 g (34.8 mmole, 58%) of the title compound as a white crystalline solid, mp 112°C.

[0089] Anal. calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.13; N, 14.13; Found: C, 60.53; H, 8.86; N, 14.04.

[0090] ^{1}H NMR δ ($CDCl_3$): 6.97 (br s, 1H, $CONH_2$), 6.91 (br t, 1H, NH), 6.29 (t, 1H, vinyl), 6.05 (br s, 1H, $CONH_2$), 2.28 (m, 2H, $CH_3\underline{CH_2}CH=$), 2.17 (m, 2H, $CH_3CH_2\underline{CH_2}$), 1.42 (m, 2H, $CH_3\underline{CH_2}CH_2$), 1.05 (t, 3H, Me), 0.93 (t, 3H, Me) ppm.

[0091] MS: 199 (MH^+, 83), 182 (MH^+ - NH_3, 79), 125 (100).

[0092] IR: 3341, 3179, 2955, 2872, 1680, 1601, 1535, 1433, 1319 cm^{-1}.

EXAMPLE 13

N-[2-n-Propylpent-(E)-2-enoyl]alanine methyl ester.

[0093] The title compound was prepared from (E)-2-enevalproyl chloride (10.95g, 68.1 mmole) and alanine methyl ester hydrochloride (10.14 g, 72.6 mmole) according to the procedure described in Ex. 4. The crude product was crystallized from hexane to give 13.25g (58.4 mmole, 86%) of a white crystalline solid, mp 25°C.

[0094] ^{1}H NMR δ ($CDCl_3$): 6.30 (br d, 1H, NH), 6.23 (t, 1H, vinyl) 4.65 (m, 1H, ala CH), 3.76 (s, 3H, OMe), 2.29 (m, 2H, $CH_3\underline{CH_2}CH=$), 2.17 (m, 2H), 1.43 (d, 3H, ala CH_3), 1.43 (m, 2H, $CH_3\underline{CH_2}CH_2$), 1.04 (t, 3H, Me), 0.92 (t, 3H, Me) ppm.

[0095] MS: 228 (MH^+, 100), 196 (NH^++ - NH_3, 100), 168 (30), 125 (76).

EXAMPLE 14

N-[2-n-Propylpent-(E)-2-enoyl]glycine-N'-methylamide.

[0096] The title compound was prepared from N-[2-n-propylpent-(E)-2-enoyl]glycine methyl ester (13.5g, 63.9 mmole), prepared from 2-enevalproyl chloride and glycine methyl ester hydrochloride as described in Ex. 5, and 35% aqueous methylamine (15 ml, 169.2 mmole), according to the procedure described in Ex. 7. The amide product was purified by column chromatography and crystallized from EtOAc to give 7.8g (36.8 mmole, 58%) of a white crystalline solid, mp 68-9°C.

[0097] Anal. caled. for $C_{11}H_2ON_2O_2$: C, 62.23; H, 9.50; N, 13.20; Found: C, 62.42; H, 9.50; N, 13.05.

[0098] ^{1}H NMR δ (DMSO): 7.94 (br t, 1H, NH) 7.67 (m, 1H, $\underline{NH}CH_3$), 6.23 (t, 1H, vinyl), 3.65 (d, 2H, gly), 2.58 (d, 3H, $NH\underline{CH_3}$), 2.21 (m, 2H, $CH_3\underline{CH_2}CH=$), 2.13 (m, 2H, $CH_3CH_2\underline{CH_2}$), 1.32 (m, 2H, $CH_3\underline{CH_2}CH_2$), 0.99 (t, 3H, Me), 0.85 (t, 3H, Me) ppm.

[0099] MS: 213 (MH^+, 73), 195 (37), 182 (MH^+ - CH^+3NH_2, 100), 125 (74).

The reaction mixture was treated with hot ethyl acetate, cooled, and filtered. The filtrate was washed consecutively with sat. $NaHCO_3$ and sat. NaCl solution, dried and evaporated to dryness. The solid residue was crystallized from ethyl acetate/hexane to give 1.50g of a white solid, mp 78-80°C.

[0117] Anal. calcd. for $C_{12}H_{24}N_2O_2$: C, 63.12, H, 10.59; N, 12.27. Found: C, 62.80, H, 10.64; N, 11.93.

[0118] ^{1}HNMR δ (DMSO): 7.73 (br t, 1H, CONH), 3.79 (d, 2H, gly), 2.84 (s, 3H, Me), 2.72 (s, 3H, Me), 2.16 (m, 1H, $(Pr)_2CH$), 1.34 (m, 2H), 1.12 (m, 6H), 0.74 (t, 6H, Me) ppm.

[0119] MS: 229 (MH^+, 100), 184 (18).

[0120] IR: 3314, 2951, 2924, 2872, 1662, 1630, 1522, 1466 cm^{-1}.

EXAMPLE 19

Biological Activity of N-(2-Propylpentanoyl)glycinamide.

[0121] All compounds provided herein were screened for their ability to protect against chemically and electrically induced convulsions, in at least two different models of epilepsy. The first model, the subcutaneous pentylenetetrazol (s.c. Met) seizure threshold test, is a standard screening procedure to show efficacy for agents against absence seizures. The second model, the maximal electroshock (MES) test, is used to show efficacy for antiepileptic agents against generalized seizures. In these studies, convulsions were inhibited or prevented in mice after intraperitoneal (i.p.) administration and/or in rats after oral (p.o.) administration of the compounds.

[0122] N-(2-Propylpentanoyl) glycinamide (hereinafter compound 1) was further tested in two additional models. The third model, electrical kindling of rats, has been known to show efficacy of antiepileptic agents against complex partial seizures that evolve into generalized motor seizures. In these tests, rats were electrically stimulated via corneal electrodes twice daily for approximately 5 days and then once daily for an additional 10 days. Once the seizure criteria, as described by R.J. Racine, et al., Electroenceph. Clin. Neurophysiol., 32: 281-294 (1972), were met, the test substance was administered p.o. to rats, and the rat electrically stimulated, and observed for the presence or absence of a seizure. In addition, compound 1 was also tested in the subcutaneous bicuculline model (s.c. Bic). For detailed procedures of all the above test models, see E.A. Swinyard, et al., in "Antiepileptic Drugs," ed. by R.H. Levy, et al., Raven Press, New York, at 85-100 (1989) and Racine, Id.

[0123] Compound 1 showed anticonvulsant activity in rodents in all of the above mentioned tests (MES, s.c. Met, s.c. Bic, and electrical kindling models). The ED50 (rat, p.o.) in the MES model was 73 mg/kg (Table 1). This value is seven times lower (more efficacious) than that found for VPA, and approximately twice that found for phenytoin (Table 1; see E.A. Swinyard, et al., id.). Further, in the electrically kindled rat model, compound 1 (administered p.o.) prevented seizures with an ED_{50} of 162 mg/kg (Table 1). The results are therefore indicative of compound 1 having an efficacy against generalized seizures and complex partial seizures which evolve into generalized motor seizures.

[0124] In addition, in the s.c. Bic model, compound 1 provided full protection from seizures in mice, at a dose that was approximately that of literature values for the ED_{50} for VPA. Literature values also show that phenytoin, considered the drug of choice for partial and generalized tonic-clonic seizures, is not effective in this model. See B.J. Wilder and R.J. Rangel, in "Antiepileptic Drugs," ed. by R.H. Levy, et al., Raven Press, New York, at 233-239 (1989).

[0125] In the s.c. Met model (mice, i.p.), the ED_{50} for compound 1 was 127 mg/kg (Table 1) as compared to the literature value of 146 mg/kg for VPA. These results further indicate efficacy for compound 1 against absence seizures as well.

EXAMPLE 20

Neurotoxicity of Compound 1.

[0126] Neurotoxicity of the claimed agents was also assessed in mice (i.p. adminstration) by the rotorod ataxia test and also in some cases in rats (p.o. administration) by the positional sense test and gait and stance test. See E.A. Swinyard, et al., in "Antiepileptic Drugs," ed. by R.H. Levy, et al., Raven Press, New York, at 85-100 (1989). None of the agents provided in the invention showed neurotoxicity in mice at the test dose of 100 mg/kg. Compound 1 had a median neurological toxic dose (TD_{50}) in rats of more than 1000 mg/kg. By comparison, the TD_{50} for VPA was 280 mg/kg. In mice, the difference between TD_{50} values between compound 1 and VPA was smaller, but still significantly higher for compound 1 (less neurotoxic) (Table 1). The protective index (PI, $PI=TD_{50}/ED_{50}$) for compound 1 in rats tested in the MES test is more than 23 times greater than that found for VPA (Table 1). These results are shown to indicate that there is a larger therapeutic dose range that can be administered before neurological side effects are usually observed.

[0127] The median lethal dose (LD_{50}) of compound 1 in mice (i.p. administration) is more than 4,000 mg/kg. This value is in contrast to VPA whose LD_{50} in the same test was 658 mg/kg. The results, therefore, indicate that compound

EXAMPLE 22

N-(2-n-Propylpentanoyl)aminoacetonitrile

[0138] A solution of valporyl chloride (3.26g, 20mmole) in toluene (20ml) was added dropwise to a stirred and ice-cooled solution of aminoacetonitrile.HCl (1.85g, 20mmole) and Et_3N (4.24g, 42mmole). The reaction mixture was stirred at ambient temperature for 3 hours; toluene (10ml) and water (10ml) were then added and the phases separated. The toluene layer was diluted in CH_2Cl_2 (80ml) and the phases separated. The organic layer was dried (magnesium sulphate) and evaporated to dryness under reduced pressure. The residue was treated with hexane (30ml, 2hr stirring at RT) and the resulting suspension was filtered and washed with hexane (10ml). The crude product was crystallized from 6:1 hexane:EtOAc to give 2.41g (13.22mmole, 66%) of a white crystalline solid; mp 76-77°C.

[0139] Anal. Calc.for $C_{10}H_{18}N_2O$: C,65.90; H,9.95; N,15.37. Found: C,65.90; H,10.22; N,15.51.

[0140] ^{1}H-NMR δ ($CDCl_3$): 6.40(br s,1H,NH), 4.19 (d,2H,CH_2), 2.19 (m,1H,$Pr_2\underline{CH}$), 1.60, 1.42 (m,4H,$CH_3\underline{CH_2}\underline{CH_2}$), 1.29 (m, 4H, $CH_3\underline{CH_2}CH_2$)

[0141] 0.90 (t, 6H, CH_3)ppm.

[0142] MS: 183(MH^+,100), 156(MH^+ -HCN,19), 127(23)
IR: 3287, 2959, 2930, 2250, 1657, 1543, 1466, 1420, 1260cm^{-1}.

EXAMPLE 23

N-(2-n-Propylpentanoyl)-N-methyl-glycine ethyl ester

[0143] A solution of-sarcosine ethyl ester.HCl (3.26g,21.2mmole) and ET_3N (4.37g, 43.3mmole) in 12ml water was added dropwise to an ice-cooled solution of valroyl chloride (3.25g, 20mmole) in CH_2Cl_2 (35ml). The mixture was stirred under reflux for 3 hours and then cooled to room temperature. The phases were separated and the organic layer was washed succesively with water (15ml), saturated sodium hydrogen carbonate (15ml) and 0.1N HCl (15ml) The residue was then dried (magnesium sulphate) and evaporated to dryness under reduced pressure affording the title compound as a yellowish oil (15.2mmole, 76%).

[0144] ^{1}H-NMR δ ($CDCl_3$): 4.18 (q,2H,Et), 4.13 (s,2H,CH_2), 3.12 (s,3H,CH_3), 2.74 (m,1H,$Pr_2\underline{CH}$), 1.65,1.35 (m,8H, $CH_3\underline{CH_2}\underline{CH_2}$), 1.27(t,3H,Et), 0.90(t,6H,CH_3)ppm.

[0145] MS: 244 (MH^+,100), 201(28), 198(25, MH^+-EtOH)

EXAMPLE 24

N- (2-n-Propylpentanoyl)-N-methyl-glycinamide

[0146] To a solution of N- (2-n-propylpentanoyl) -N-methyl-glycine ethyl ester (1.0g, 4.1mmole) in 3ml ethanol, 6.8ml of aqueous ammonium hydroxide was added. The reaction mixture was stirred under reflux for 15 hours and evaporated to dryness under reduced pressure. The residue was taken up in EtOAC(5ml) and the solution washed with aqueous sodium hydrogen carbonate (5ml), 0.1N HCl (2x5ml) and finally with saturated NaCl(5ml), dried (magnesium sulphate) and evaporated to dryness under reduced pressure. The crude product was treated with hexane (2x2ml), filtered and dried to give 120mg(14%) of the title compound as a white solid; mp 138-140°C.

[0147] ^{1}H-NMR δ ($CDCl_3$): 6.32 (br s,1H,$CONH_2$), 5.45 (br s,1H,$CONH_2$), 4.02 (d,2H,glyCH_2), 3.17 (s,3H,NCH_3), 2.70 (m,1H, $Pr_2\underline{CH}$), 1.60,1.40 (m, 4H, $CH_3\underline{CH_2}\underline{CH_2}$) , 1.25 (m, 4H, $CH_3\underline{CH_2}CH_2$) , 0.90 (t,6H,CH_3).

[0148] MS: 215(MH^+,100), 198(MH^+-NH_3,46), 172(5), 158(9).

EXAMPLE 25

[0149] Various compounds were tested for biological activity and neurotoxicity in the maximal electroshock (MES) test and subcutaneous pentylenetetrazol (s.c. Met) seizure threshold models, in mice (ip), rats (p.o.) or both as indicated, according to the procedures of Examples 19 and 20. Experimental results are presented in Table 4.

Table 2: Activity scores of rats chronically treated with compound 1.

Treatment	Day activity 14.00-20.00h		Night activity 20.00-08.00h	
	Big mov.	Total mov.	Big mov.	Total mov.
Control (7)	1939±349	6391±983	6124±489	23750±2075
compound 1 (7)	2402±307	7749±1188	7217±765	22568±2209
Na Valproate 500mg/kg(6)	2784±352	8963±1554	5832±854	18876±2039

Activity scores of drug-treated rats, measured in activity cages on days 8-9 after initiation of daily oral dosing with the given drug. Figures are number of crossings±SEM. Number of rats per group are given in parenthesis.

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Table 4. Biological activity and neurotoxicity of various claimed compounds.

COMPOUND	MICE (ip)			MICE (ip)		
	MES			scMet		
	ED50	PI	TD50	ED50	PI	TD50
1	152	2.4	370	127	2.9	370
3	<300		>1	>300		
8	207	1.5	315	108	2.9	315
2	170	1	170	154	<1	170
9	<100	>1	>100	>100	1	>100
12	80	2.9	230	150	1.5	230
14	107	1.5	157	131	1	157
18	<300		<300	<300		<300
22	<100	>1	>100	<100	>1	>100

Table 4 (cont'd)

COMPOUND	RAT (po)			RAT (po)		
	MES			scMet		
	ED50	PI	TD50	ED50	PI	TD50
1	73	13.7	1000	250	4	1000
8	75	2	150			
12	60	8.3	500	250	2	500

Values are given in mg/kg. The compounds are identified by their example number (e.g., compound 22 is N-(2-n-Propylpentanoyl)aminoacetonitrile, disclosed in synthesis Example 22.)

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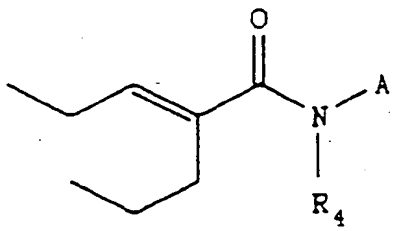
5. The compound of claim 1, wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group.

6. The compound of claim 1, wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indclyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

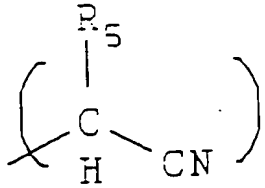
7. A compound of claim 1 selected from the group consisting of:

N-(2-n-propylpentanoyl)glycinamide;
N-(2-n-propylpentanoyl)-N-methyl-glycinamide;
N-(2-n-propylpentanoyl)glycine-N'-methylamide;
N-(2-n-propylpentanoyl)glycine-N'-butylamide;
N-(2-n-propylpentanoyl)leucinamide;
N-(2-n-propylpentanoyl)alanine-N'-benzylamide;
N-(2-n-propylpentanoyl)alaninamide;
N-(2-n-propylpentanoyl)-2-phenylglycinamide;
N-(2-n-propylpentanoyl)threoninamide;
N-(2-n-propylpentanoyl)glycine-N',N'-dimethylamide;
and N-(2-n-propylpentanoyl) aminoacetonitrile.

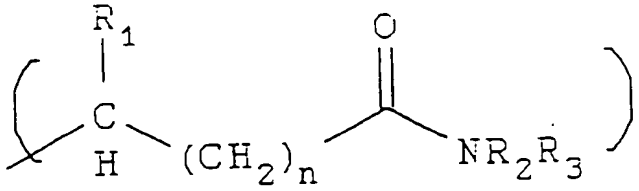
8. A compound having the structure:



wherein A is X or Y,
X comprises



Y comprises



;

25. Use of a compound according to any of Claims 1-14 in the manufacture of a medicament for the treatment of neurotoxic injury.

26. Use of a compound according to any of Claims 1-14 in the manufacture of a medicament for the treatment of convulsions in a subject afflicted with epilepsy.

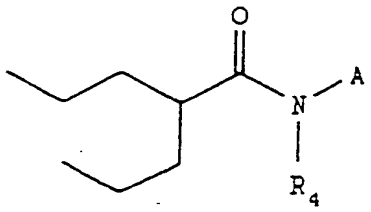
27. Use of a compound according to any of Claims 1-14 in the manufacture of a medicament for the treatment of stroke.

28. Use of a compound according to any of Claims 1-14 in the manufacture of a medicament for the treatment of brain ischemia.

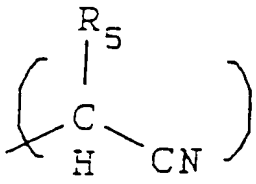
29. Use of a compound according to any of Claims 1-14 in the manufacture of a medicament for the treatment of head trauma injury.

Patentansprüche

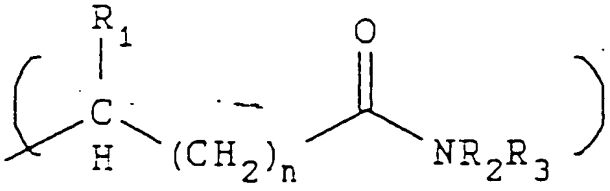
1. Verbindung der Struktur



in der A X oder Y bedeutet,
X umfaßt

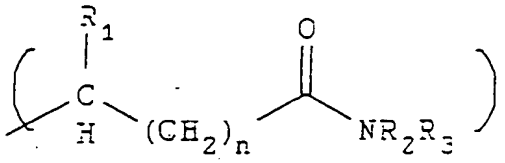


Y umfaßt



R_1, R_2, R_3, R_4 und R_5 unabhängig voneinander

Wasserstoff
eine C_1-C_6-Alkylgruppe
eine Aralkylgruppe, oder
eine Arylgruppe bedeuten,



R_1, R_2, R_3, R_4 und R_5 unabhängig voneinander

Wasserstoff
eine C_1-C_6-Alkylgruppe
eine Aralkylgruppe, oder
eine Arylgruppe bedeuten,

und n 0, 1, 2 oder 3 bedeutet.

9. Verbindung nach Anpruch 8, in der

A Y, und
R_4 Wasserstoff
bedeutet.

10. Verbindung nach Anspruch 8, in der die C_1-C_6-Alkylgruppe eine geradkettige Alkylgruppe ist.

11. Verbindung nach Anspruch 8, in der die C_1-C_6-Alkylgruppe eine verzweigtkettige Alkylgruppe ist.

12. Verbindung nach Anspruch 8, in der die Aralkylgruppe eine Benzyl-, Alkylbenzyl-, Hydroxybenzyl-, Alkoxycarbonylbenzyl-, Aryloxycarbonylbenzyl-, Carboxybenzyl-, Nitrobenzyl-, Cyanobenzyl- oder Halogenbenzylgruppe ist.

13. Verbindung nach Anspruch 8, in der die Arylgruppe eine Phenyl-, Naphthyl-, Anthracenyl-, Pyridinyl-, Indolyl-, Furanyl-, Alkylphenyl-, Hydroxyphenyl-, Alkoxycarbonylphenyl-, Aryloxycarbonylphenyl-, Nitrophenyl-, Cyanophenyl-, Halogenphenyl-, Mercaptophenyl- oder Aminophenylgruppe ist.

14. Verbindung nach Anspruch 8, ausgewählt aus der Gruppe:

N-(2-n-Propylpent-2-enoyl)-glycinamid
N-(2-n-Propylpent-2-enoyl)-alaninamid, und
N-(2-n-Propylpent-2-enoyl)-glycin-N'-methylamid.

15. Pharmazeutische Zubereitung umfassend die Verbindung der Ansprüche 1 oder 8 oder ein pharmazeutisch annehmbares Salz hiervon in einer therapeutisch wirksamen Menge und einen pharmazeutisch annehmbaren Trägerstoff.

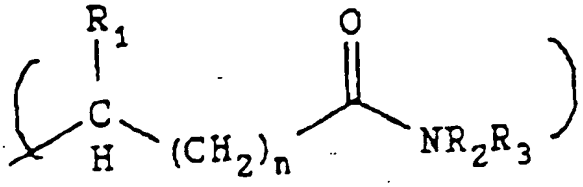
16. Pharmazeutische Zubereitung nach Anspruch 15, in der die therapeutisch wirksame Menge eine Menge von 10 bis 500 mg ist.

17. Pharmazeutische Zubereitung nach Anspruch 16, in der der Trägerstoff ein Feststoff und die Zubereitung eine Tablette ist.

18. Pharmazeutische Zubereitung nach Anspruch 16, in der der Trägerstoff ein Gel und die Zubereitung ein Suppositorium ist.

19. Pharmazeutische Zubereitung nach Anspruch 16, in der der Trägerstoff eine Flüssigkeit und die Zubereitung eine Lösung ist.

20. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 14 bei der Herstellung eines Medikaments zur Behandlung der Epilepsie.



R_1, R_2, R_3, R_4 et R_5 représentent chacun indépendamment

un atome d'hydrogène,
un groupe alkyle en C_1 à C_6,
un groupe aralkyle, ou
un groupe aryle ;

et n vaut 0.

2. Composé selon la revendication 1, dans lequel

A est Y ; et
R_4 est un atome d'hydrogène.

3. Composé selon la revendication 1, dans lequel le groupe alkyle en C_1 à C_6 est un groupe alkyle à chaîne linéaire.

4. Composé selon la revendication 1, dans lequel le groupe alkyle en C_1 à C_6 est un groupe alkyle à chaîne ramifiée.

5. Composé selon la revendication 1, dans lequel le groupe aralkyle est un groupe benzyle, alkylbenzyle, hydroxybenzyle, alcoxycarbonylbenzyle, aryloxycarbonylbenzyle, carboxybenzyle, nitrobenzyle, cyanobenzyle, ou halogénobenzyle.

6. Composé selon la revendication 1, dans lequel le groupe aryle est un groupe phényle, naphtyle, anthracényle, pyridinyle, indolyle, furanyle, alkylphényle, hydroxyphényle, alcoxycarbonylphényle, aryloxycarbonylphényle, nitrophényle, cyanophényle, halogénophényle, un groupe mercaptophényle ou aminophényle.

7. Composé selon la revendication 1 choisi dans le groupe formé par :

le N-(2-n-propylpentanoyl)glycinamide ;
le N-(2-n-propylpentanoyl)-N-méthylglycinamide ;
le N-(2-n-propylpentanoyl)glycine-N'-méthylamide ;
le N-(2-n-propylpentanoyl)glycine-N'-butylamide ;
le N-(2-n-propylpentanoyl)leucinamide ;
le N-(2-n-propylpentanoyl)alanine-N'-benzylamide ;
le N-(2-n-propylpentanoyl)alaninamide ;
le N-(2-n-propylpentanoyl)-2-phénylglycinamide;
le N-(2-n-propylpentanoyl)thréoninamide ;
le N-(2-n-propylpentanoyl)glycine-N',N'-diméthylamide ;
et le N-(2-n-propylpentanoyl)aminoacétonitrile.

8. Composé ayant la structure :

trophényle, cyanophényle, halogénophényle, un groupe mercaptophényle ou aminophényle.

14. Composé selon la revendication 8, choisi dans le groupe formé par :

le N-(2-n-propylpent-2-énoyl)glycinamide ;
le N-(2-n-propylpent-2-énoyl)alaninamide ; et
le N-(2-n-propylpent-2-énoyl)glycine-N'-méthylamide.

15. Composition pharmaceutique qui comprend le composé selon la revendication 1 ou 8 ou un sel de celui-ci acceptable sur le plan pharmaceutique en une quantité efficace sur le plan thérapeutique et un véhicule acceptable sur le plan pharmaceutique.

16. Composition pharmaceutique selon la revendication 15, dans laquelle la quantité efficace sur le plan thérapeutique est une quantité allant de 10 à 500 mg.

17. Composition pharmaceutique selon la revendication 16, dans laquelle le véhicule est une substance solide et la composition est un comprimé.

18. Composition pharmaceutique selon la revendication 16, dans laquelle le véhicule est un gel et la composition est un suppositoire.

19. Composition pharmaceutique selon la revendication 16, dans laquelle le véhicule est un liquide et la composition est une solution.

20. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement de l'épilepsie.

21. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement d'une psychose.

22. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement de troubles cognitifs.

23. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement de maladie de neurodégénérescence.

24. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement d'une dyskinésie.

25. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement d'une lésion neurotoxique.

26. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement de convulsions chez un sujet atteint d'épilepsie.

27. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement d'un ictus.

28. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement d'une ischémie cérébrale.

29. Utilisation d'un composé selon l'une quelconque des revendications 1 à 14, dans la fabrication d'un médicament destiné au traitement d'une lésion traumatique à la tête.

FIGURE 1

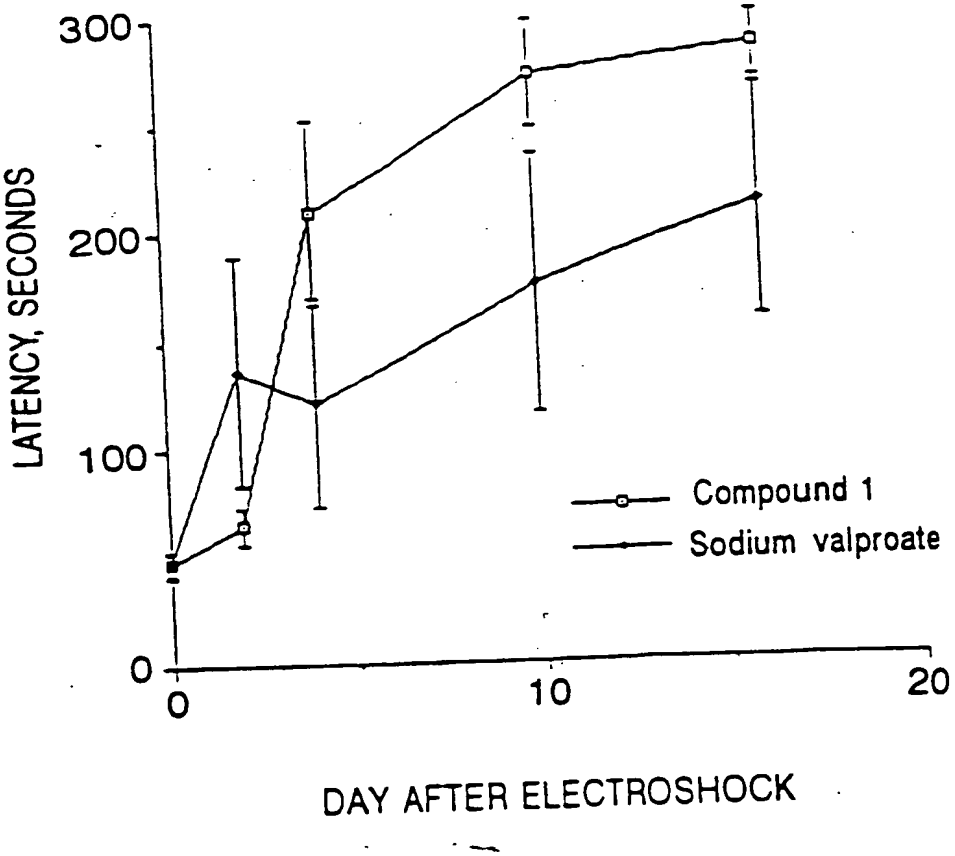
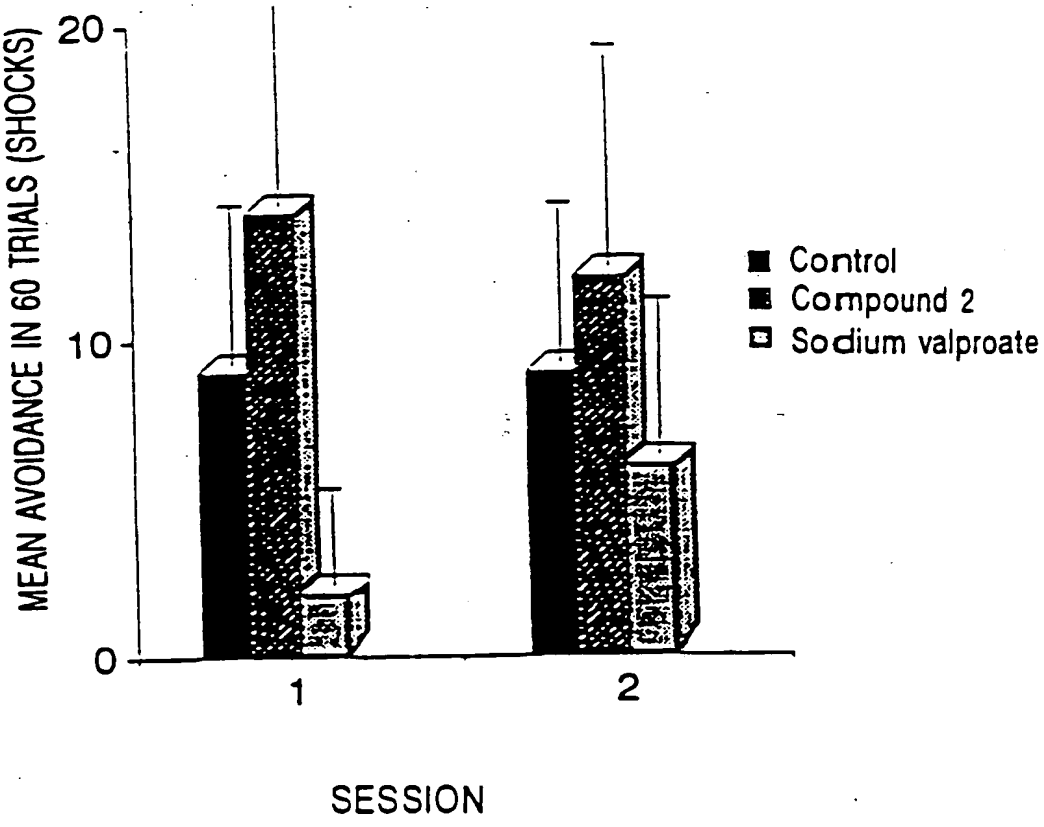

300
200
100
0
LATENCY, SECONDS
0
10
20
DAY AFTER ELECTROSHOCK
Compound 1
Sodium valproate

FIGURE 2


MEAN AVOIDANCE IN 60 TRIALS (SHOCKS)
20
10
0
1
2
SESSION
Control
Compound 2
Sodium valproate